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The effect of Saffron on weight and lipid profile: A systematic review, meta-analysis and dose-response of randomized clinical trials

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Abbreviations

LDL Low-density lipoprotein

HDL High-density lipoprotein

TG Triglycerides

DM Diabetes

CVD Cardiovascular disease

Abstract

Plant derivatives such as carotenoids and phytosterols enrich foods have been shown to reduce plasma Triglyceride (TG), low density lipoprotein cholesterol (LDL), and cholesterol concentrations. The aim of this systematic review and meta-analyses study was investigation the effects of saffron on lipid profiles, reported in Randomized Control Trials. We performed a systematic electronic search in PubMed/MEDLINE, Cochrane and SCOPUS to identify randomised controlled trials and screening of relevant articles references up to October 12th, 2018. There were no language restrictions. We performed this systematic review and meta-analysis according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. we identified and analyzed fourteen eligible studies in this meta-analysis. Our study found a significant reduction in cholesterol and triglycerides following saffron intervention (Weighted mean difference [WMD]: -6.36 mg/dl, 95% CI: -10.58, -2.18) and (WMD: -5.37 mg/dl, 95% CI: -10.25, -0.48), respectively. There was no significant effect on Weight and LDL concentration. A meta regression analysis showed that Long-term saffron intervention can increase the HDL levels. In conclusions, our study findings indicate some benefits of saffron on cholesterol, HDL, and triglycerides compared to placebo. However, we recommend the conduct of adequately powered, high quality RCTs with short and long-term follow up, evaluating relevant clinical outcomes to allow for making definitive recommendations.

Keywords: Saffron; Crocin; weight; Triglyceride; Cholesterol; LDL

Introduction

The most common strategies for the prevention or reversal of obesity, and many associated blood lipid disorders, are dietary control or manipulation, and physical activity. However, in recent years the interest in the utility of conjunctive or alternative therapies has proliferated. Of contemporary interest are dietary phytochemicals, which are ostensibly considered therapeutic agents to counter obesity, and associated dyslipidemia (Baboota et al., 2013; Hasani-Ranjbar, Larijani, & Abdollahi, 2009). Such compounds utilize anti-obesity properties by regulating lipid absorption, modulating energy intake and expenditure, decreasing lipogenesis and increasing lipolysis, and differentiating the proliferation of pre-adipocytes (González-Castejón & Rodriguez-Casado, 2011). Saffron, Crocus sativus L., belongs to the

Iridaceae family, and is a common plant widely cultivated in Iran, India and the Mediterranean. Moreover, a variety of biologically active ingredients have been isolated from saffron. It is accepted that crocin (monoglycosyl or diglycosyl esters of crocetin), crocetin (a natural carotenoid dicarboxylic acid precursor of crocin), picrocrocin (monoterpene glycoside precursor of safranal), and safranal (the major organoleptic principle of the stigmas) comprise the four major bioactive compounds of saffron and are responsible not only for its sensory profile but also for its health-promoting properties (Ochiai et al., 2007; Xiang, Qian, Zhou, Liu, & Li, 2006). In recent decades, saffron has been asserted to, purportedly, possess many therapeutic properties, with growing evidence that saffron has a conceivable anti-obesity, therapeutic effect (Mashmoul, Azlan, Khaza'ai, Yusof, & Noor, 2013). Saffron contains a rich source of carotenoids (crocin), glycoside (picrocrocin) and a volatile oil component (safranal) (Fernández, 2004; WINTERHALTER & STRAUBINGER, 2000). Crocin, one of the major bioactive constituents, and has a plethora of biological activities, including antigenotoxic and cytotoxic effects (Abdullaev, 2006; G Gutheil, Reed, Ray, Anant, & Dhar, 2012), antioxidant (Charles, 2013; Chen et al., 2008), antinociceptive and anti-inflammatory (Poma, Fontecchio, Carlucci, & Chichiricco, 2012), anti atherosclerotic (Kamalipour & Akhondzadeh, 2011), anti-diabetic (Shirali, Zahra Bathaie, & Nakhjavani, 2013), hypotensive (Imenshahidi, Hosseinzadeh, & Javadpour, 2010), hypolipidaemic(Sheng, Qian, Zheng, & Xi, 2006), hypoglycemic (Kianbakht & Mozaffari, 2009; Mohajeri, Mousavi, & Doustar, 2009), antidepressant(Gout, Bourges, & Paineau Dubreuil, 2010; Sahraian, Jelodar, Javid, Mowla, & Ahmadzadeh, 2016) and satiety enhancing (Gout et al., 2010). There is a general consensus on the positive, supporting role of saffron, or its active constituents, in modulating serum total cholesterol (TC), total triglyceride (TG), low density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) (Arasteh et al., 2010; Hoshyar et al., 2016; Samarghandian, Azimi Nezhad, & Samini, 2014; Shirali et al., 2013). In an in vitro study, crocetin decreased the levels of Reactive Oxygen Species, free radical-mediated lipid peroxidation, and increased radical scavenging activity (Xiang et al., 2006). Furthermore, saffron has been reported to possess anti-inflammatory properties (Ochiai et al., 2007). Saffron reportedly improves the lipid profile and increases glucose uptake by an insulin dependent pathway that stimulates phosphorylation of AMP-activated protein kinases (AMPK), acetyl-CoA carbohydrate (ACC), and mitogen activated protein kinases (MAPKS); whilst, co-treatment of saffron and insulin has been shown to improve insulin sensitivity (Kang et al., 2012), albeit in animal or invitro models. When extended into human investigations, Saffron, or its constituents, has been shown to elicit positive effects on the blood lipid profile and weight

status. For instance, Gout et al (2010) reported significant body weight reductions(Gout et al., 2010), following a period of supplementation with a Saffron constituent, whilst, Kermani et al (2017) noted improvements in HDL levels and on serum pro-oxidant balance(Tayyebe Kermani et al., 2017), and Abedimanesh et al (2017) reported significant decreases in body mass index (BMI), waist circumference and fat mass values. However, compared to animal models, the literature is far more equivocal as to its effect in humans(Nasim Abedimanesh et al., 2017). Among others, Javandoost et al (2017), in a Randomized Control Trial, reported no significant changes in LDL, HDL or TG following supplementation(Ali Javandoost et al., 2017); similarly, Milajerdi et al (2018) found no statistical difference in other metabolic parameters such as serum lipids, blood pressure, and HbA1c(Alireza Milajerdi et al., 2018). Notwithstanding the equivocality in human studies, no meta-analyses has been conducted to investigate the overall therapeutic effect of saffron, taking into consideration important aspects, such as dosage and supplementation period. Furthermore, given the potential of Saffron, or its constituents, to elicit positive reparative or preventative effects, and compliment traditional therapies, the aim of this study was to systematically review and meta analyses the effects of saffron on lipid profiles, reported in Randomized Control Trials.

Methods

Study design and Search strategy

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statements(Moher et al., 2015). We performed a systematic electronic search in PubMed/MEDLINE, Cochrane and SCOPUS to identify randomised controlled trials (RCTs) assessing the effects of saffron on lipid profile (cholesterol, TG, HDL and LDL) compared with no intervention (placebo) among clinical population. We used the Boolean search terms (AND, OR, or NOT) in order to create the search strategy, merging the search terms of the exposure (saffron therapy) and the outcomes (Weight, cholesterol, TG, HDL and LDL). The search strategy was developed using a specific approach, including all the items from database inception until October 12th, 2018 and without using language restrictions. The details of the search strategy are reported in the Supplemental Table 1.

Selection criteria

The PICOS criteria was used to select articles suitable for inclusion. All identified studies were obtained from each database were stored in Endnote Reference Manager X8© and duplicates were excluded using the Endnote function "remove duplicates". Two authors (JR and NM) independently reviewed the titles, abstracts and full-texts of relevant articles to identify eligible studies. The criteria for study selection included the following: 1) Adult subjects (18 years and older); 2). RCT studies reporting mean differences (WMD) with the 95% confidence intervals (95% CI); 3). Studies that evaluated the effects of Saffron, Crocin, or Saffron extract on weight and lipid profile. The exclusion criteria included studies evaluating: 1) Treatments other than Saffron; 2) Outcomes other than participants weight and lipid profile; 3) Animal studies; 4) Studies without a placebo group or using no-randomised study designs 5) Conference abstracts, casereports, reviews, commentaries.

Data extraction

Two reviewers (JR and NM) independently extracted data from each study included in the review using a standardised data extraction form. Discrepancies were resolved by discussion with a senior author (PM). The information extracted in the form included the following: study authors, year of publication, geographic location, duration of follow up, sample size, mean age (y), saffron Dose (mg/d), and mean and standard deviation (SD) of outcome in pre- and post-intervention. Quality assessment Studies included were assessed for their quality using the "Cochrane collaboration's tool for quality assessment of randomized control trials" (Higgins et al., 2011), which considers the following characteristics: Selection bias (random sequence generation and allocation concealment), completeness of outcome data, other sources of bias, blinding of assessors and participants (performance bias and Outcome bias), and attrition bias. Each study was categorised as having a low, high or unclear risk of bias for each characteristic. Each study was ranked as having poor, fair or good quality according to the AHRQ Standards (Higgins et al., 2011). Studies were judged to be of poor quality when the random sequence generation, allocation concealment and blinding showed high or unclear risk of bias.

Statistical analysis

We assessed the effects of Saffron on lipid profile using weighted mean differences (WMD) with the 95% CI. When the SD of the mean difference for studies was not reported it was calculated by the following formula: [SD2 baseline + SD2 final – (2R x SD baseline x SD

final)] SD2 baseline + SD2 final – (2 R* SD baseline + SD final) (Cooper, Hedges, & Valentine, 2009). The random-effects model (DerSimonian and Laird method) was used to calculate the pooled weighted mean difference (WMD). In accordance with the Cochrane thresholds recommendations, we used the Qtest, the I-squared and an alpha level of 0.05 for statistical significance to assess the heterogeneity across studies, (Green & Higgins, 2005). Subgroup analyses were used to identify potential causes of heterogeneity among the articles. The type of Saffron (Saffron, Crocin, or Saffron extract) was considered as a predefined source of heterogeneity. Sensitivity analysis was performed to investigate the effect of each study on overall analysis. We used the funnel plot and the Egger's weighted regression tests to evaluate the likelihood of publication bias. The nonlinear potential effects of Saffron dosage (mg/day) were examined using fractional polynomial modelling. Metaregression was used to determine effect of duration of intervention on outcomes. All statistical tests were conducted using the STATA 14 (StataCorp LP, College Station, USA), using a p value of 0.05 for statistical significance.

Results:

We identified 135 published articles using our search strategy from PubMed, Scopus, and Cochrane Library (Supplementary Figure 1). After, removing duplicates, 96 studies were screened for eligibility. Seventy-two articles were excluded based on title and abstract. Ten other studies because of the following reasons: 1) Non-RCT design (n=5), 2) Animal trials (n=3), and 3) Studies that evaluated the effect of Saffron in combination with other foods and supplements (n=2). Fourteen articles (18 arms) representing 788 participants (N. Abedimanesh et al., 2017; Azimi, Ghiasvand, Feizi, Hariri, & Abbasi, 2014; Fadai et al., 2014; Gout et al., 2010; Jafarnia et al., 2017; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Mansoori et al., 2011; A. Milajerdi et al., 2018; Modaghegh, Shahabian, Esmaeili, Rajbai, & Hosseinzadeh, 2008; Mohamadpour, Ayati, Parizadeh, Rajbai, & Hosseinzadeh, 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018) met our inclusion criteria and were included in the meta-analysis. Study characteristics Characteristics of eligible studies are shown in Table 1. Most studies were conducted in the Iran (N. Abedimanesh et al., 2017; Azimi et al., 2014; Fadai et al., 2014; Jafarnia et al., 2017; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Mansoori et al., 2011; A. Milajerdi et al., 2018; Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018) and one in France

(Gout et al., 2010). The sample size of the included studies ranged from 20 to 81 individuals with mean age of 43 years in intervention groups and 45 years in control groups. The mean duration of the study interventions was 7 weeks (from 1 to 12 weeks). Articles were published across a 10-year duration, between 2008 and 2018. The mean dose of the Saffron administered was 160 mg/day (5 to 1000 mg/day).

Quality assessment

The results of the quality assessment of included studies are provided in Table 2. Four arms have fair quality (Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016), one has poor quality (Azimi et al., 2014), and thirteen have good quality (N. Abedimanesh et al., 2017; Fadai et al., 2014; Gout et al., 2010; Jafarnia et al., 2017; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Mansoori et al., 2011; A. Milajerdi et al., 2018; Sepahi et al., 2018). Most studies demonstrated adequate quality for key factors. Only four studies were rated as having an unclear risk of bias for random sequence generation or allocation concealment.

Meta-analysis results

Body Weight Six arms providing a total of 299 participants (intervention = 164, and control= 135) reported changes in weight as an outcome measure (N. Abedimanesh et al., 2017; Azimi et al., 2014; Gout et al., 2010; Jafarnia et al., 2017; T. Kermani, T. Kazemi, et al., 2017). We combined the results using the random-effects model and showed insignificant reduction in weight following Saffron intervention (WMD: -0.43 kg, 95% CI: -1.33, 0.46) (Fig 1.). There was significant heterogeneity among studies (p=0.001). Cholesterol Sixteen studies providing a total of 619 participants (intervention= 353, and control= 266) reported cholesterol as an outcome measure (N. Abedimanesh et al., 2017; Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Mansoori et al., 2011; A. Milajerdi et al., 2018; Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). Pooled results from the random effects model showed that cholesterol levels reduced in the intervention group compared with the control group (WMD: -6.36 mg/dl, 95% CI: -10.58, -2.18). There was a significant heterogeneity among studies (p=0.001). TG Sixteen studies providing a total of 640 participants (intervention = 353, and control = 287) reported TG as an outcome measure (N.

Abedimanesh et al., 2017; Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Mansoori et al., 2011; A. Milajerdi et al., 2018; Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). We pooled results using the random-effects model and showed that TG levels reduced in the Saffron group compared with the control group (WMD: -5.37 mg/dl, 95% CI: -10.25, -0.48). There was significant heterogeneity among studies (p=0.001). LDL Fifteen studies providing a total of 620 participants (intervention= 343, and control= 277) reported LDL as an outcome measure (N. Abedimanesh et al., 2017; Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). Compared with the placebo group, administering Saffron as intervention was not associated with a significant reduction in LDL levels (WMD: -3.03 mg/dl, 95% CI: -6.53, 0.47). We found significant heterogeneity among the studies (p= 0.001). HDL Pooled results from fifteen studies (N. Abedimanesh et al., 2017; Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018) using the random-effects model indicated that Saffron as intervention resulted in non-significant increase in HDL levels (WMD: 0.91 mg/dl, 95% CI: -0.13, 1.96) with significant heterogeneity among the studies (p= 0.01).

Subgroup analysis, Meta-regression, and Non-linear dose-responses

The results of the subgroup analyses are summarized in Table 3. We stratified studies based on type of Saffron (Saffron or Crocin). This analyses showed that TG levels (WMD: -11.36 mg/dl, 95% CI: -19.64, 3.07) decreased significantly when Saffron was used as intervention compared with trials that used Crocin (WMD: -0.42 mg/dl, 95% CI: -6.07, 5.21). However, the subgroup analyses by type of Saffron (Saffron or Crocin) did not have significant effect on change in weight, cholesterol, LDL, and HDL. Subgroup analysis based of the disease type of the participants showed this variable was not source of heterogeneity between studies. We performed a meta-regression analysis to examine the variation in treatment effect of Saffron based on duration of intervention. The meta-regression analysis suggested that duration of intervention was a significant sources of trial heterogeneity for HDL changes (p=0.03, Coef:0.5308) (Supplemental Fig 2). Although, the duration of intervention did not demonstrate

any significant changes in cholesterol and TG levels, the results showed an indirect relation between them. Also, meta-regression analysis of duration of intervention showed no significant effect on LDL and weight. We explored the dose-response relationship between dose of Saffron (mg/day), TG (Pnonlinearity = 0.04, Coef=-11.1094) and cholesterol (Pnonlinearity = 0.01, Coef=-11.3923) (Fig 2). The TG and cholesterol reduction trend continues until 400 mg/day of Saffron dose and then this effect reversed. Evaluating the dose-response relationship based on dose of Saffron showed no significant effect on LDL and weight.

Publication bias and Sensitivity analysis

The Egger's and Begg tests did not show publication bias for weight (p=0.32, p=0.34) and HDL (p=0.15, p=0.45) (Supplemental Fig 3). Begg tests did not show any publication bias for cholesterol (p=0.75), TG (p=0.72), and LDL (p=0.40) too. We identified significant publication bias for cholesterol (p=0.01), TG (p=0.03), and LDL (p=0.06) when using the Egger's test 'trim and fill' method for adjusting for publication bias (Supplemental Table 2). The results of our sensitivity analysis did not show significant differences beyond the limits of 95% CI of calculated SESs for Saffron intervention studies (Supplemental Fig 4).

Discussion

This systematic review and meta-analysis aimed to estimate the effect of Saffron as a health intervention on lipid profile. The evidence provided in this review summarizes the literature using high quality evidence from randomized controlled trials investigating the effects of Saffron on weight, cholesterol, TG, LDL, and HDL. We found evidence to suggest a reduction in cholesterol and TG levels when saffron was administered compared to treatment with placebo. The evidence from these studies was judged to be of poor quality due to inadequate description of randomisation or allocation concealment. Also, the clinical relevance of the differences demonstrated by cholesterol and TG as biomarkers among participants is unclear. These findings are similar to results from other published reviews supporting the therapeutic role of saffron on triglyceride and cholesterol (Ghaffari & Roshanravan, 2018) (20). A number of studies (Bathaie & Mousavi, 2010; Bukhari, Manzoor, & Dhar, 2018; Christodoulou, Kadoglou, Kostomitsopoulos, & Valsami, 2015; Melnyk, Wang, & Marcone, 2010) have reported the preventive and therapeutic benefits of Saffron through its hypotensive, hypo-lipidemic and anti-oxidative properties. These effects are demonstrated via a number of

pathways. Saffron decreases systolic blood pressure and mean arterial pressure (Ghaffari & Roshanravan, 2018) through it vaso-modulating effects and anti-inflammatory effects. It also exerts it therapeutic effects via its lipid-lowering effects (Shafiee et al., 2017). Other mechanisms of action include regulating the expression of growth factors such as adiponectin, tumor necrosis factor (TNF) α and leptin in adipose tissue or fat mass (Ghaffari & Roshanravan, 2018). However, there was no evidence from this review to support the use of saffron for promoting weight loss and LDL compared to the placebo. Due to the nature of the evidence evaluating this outcomes and significant clinical differences identified between studies, clinical recommendations from this review is uncertain. Previous reviews evaluating the effects of saffron have reported evidence to support the beneficial effects for weight, HDL and LDL (Bukhari et al., 2018; Ghaffari & Roshanravan, 2018; Rahaiee, Moini, Hashemi, & Shojaosadati, 2015; Shafiee et al., 2017). However, most of the evidence from these reports are from animal studies and do not provide evidence of causal effects. Few of these provide evidence from clinical studies or supported by evidence from randomized controlled trials in humans with demonstrable clinical applications. The mechanism of action for the therapeutic effects of saffron are varied. For obesity the expression of digestive enzymes is downregulated. Saffron inhibits the secretion of pancreatic and gastric lipases which regulate fat absorption, decreasing the storage of central adipose tissue and blood circulating leptin levels. This results in an increased feeling of satiety (Shafiee et al., 2017). The lipid-lowering effects of Saffron have also been linked to the modulation of the oxidation of lipoproteins via its anti-oxidative properties (Ghaffari & Roshanravan, 2018). We identified sufficient number of studies that allowed for the evaluation of sources of heterogeneity. A sub group analysis by type of saffron and the disease type of the participants showed no further changes on weight, cholesterol, LDL, and HDL. An increased effect on TG was evident when the analysis was sub-grouped type of saffron (Saffron or Crocin). This finding is supported by consistent evidence from literature reviews suggesting greater effects when saffranal compound is used compared to crocin(Melnyk et al., 2010). There is a possibility that the concentration and combination of the components of saffron inhibit mechanistic pathways more readily than crocin. We found a linear dose-dependent relationship between dose of Saffron (mg/day), TG and cholesterol. We found no dose-response relationship for weight, HDL and LDL. But this finding may be masked by the size and quality of studies analyzed. Furthermore, a sub group analysis by duration of the intervention showed duration as a significant source of heterogeneity for HDL, suggesting that clinical administration for longer durations may prove beneficial. However, we did not observe similar changes for weight, cholesterol, LDL and TG levels. There are a number

of limitations with this review. Although we did not identify publication bias for outcomes we explored, we did not explore the grey literature. The review was conducted using a specific search strategy, which may have limited the result of the articles found. Also, we used data from studies with small sample sizes, significant clinical heterogeneity and varying levels of the quality of the evidence, may have masked significant findings on the effect of saffron or variation due to systematic error. Also, the varying nature of the intervention dosage and durations explored in studies included in this review limited adequate clinical comparability and application. This limited the strength of the clinical recommendations. A maximum tolerated dose of 1.5g/day for saffron has been recommended as safe levels (Ghaffari & Roshanravan, 2018). The range for the doses of saffron administered in studies included in this review was 5mg/day to 1000mg/day and no major adverse events or toxic reactions were reported. None of the studies included in this review provided further information on the safety profile of saffron or crocin to aid their use as a clinical therapeutic agent(N. Abedimanesh et al., 2017; Azimi et al., 2014; Fadai et al., 2014; Gout et al., 2010; Jafarnia et al., 2017; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Mansoori et al., 2011; A. Milajerdi et al., 2018; Modaghegh et al., 2008; Mohamadpour et al., 2013; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). the quality of the evidence identified limits recommendation of saffron for clinical management.

Conclusion

There is some evidence from randomised controlled trials to support the use of variants of saffron among patients and healthy participants. We identified some benefits on cholesterol and triglycerides compared to placebo. However, we suggest caution in the interpretation of these results due to the strength of the evidence informing this recommendation and the unclear clinical application. We found no difference for the use of saffron on weight, low and high density lipo-proteins compared to placebo. We recommend the conduct of adequately powered, high-quality RCTs with short and long-term follow up, evaluating relevant clinical outcomes to allow for making definitive recommendations. Future studies should explore the mechanistic pathways of saffron in humans, this is still not fully understood. Varying doses of saffron should be compared to confirm its efficacy using standardised methods for administering the extract and measuring outcomes.

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Table 1. Baseline Characteristics of Included Studies in the Meta-analysis

Studies	Author	Country	Year	Follow-up, (W)	Patients, (n) Int/~~Pla~~Plc		Mean age, (y) Int/~~Pla~~Plc		Saffron Dose (mg/d)	Type of Saffron	Type of participants disease~~Type of population~~	Biomarker
1	Sepahi	Iran	2018	12	23	20	54	57	5	Crocin	DM	Cholesterol, TG, LDL, HDL
2	Sepahi	Iran	2018	12	23	20	56	57	15	Crocin	DM	Cholesterol, TG, LDL, HDL
3	Nikbakht-Jam	Iran	2016	8	30	29	41	-	30	Crocin	sMet	Cholesterol, TG, LDL, HDL
4	Mohamadpour	Iran	2013	4	22	20	31	-	200	Crocin	healthy	Cholesterol, TG, LDL, HDL
5	Modaghegh	Iran	2008	1	10	10	27	27	200	Saffron	healthy	Cholesterol, TG, LDL, HDL
6	Modaghegh	Iran	2008	1	10	10	28	28	400	Saffron	healthy	Cholesterol, TG, LDL, HDL
7	Milajerdi	Iran	2018	8	27	26	54	55	30	Saffron	DM	Cholesterol, TG, LDL, HDL
8	Mansoori	Iran	2011	4	10	10	35	42	30	Saffron	Depression	Cholesterol, TG
9	Kermani	Iran	2017	12	22	22	43	42	100	Saffron	sMet	Weight, Cholesterol, TG, LDL, HDL
10	Kermani	Iran	2017	6	22	22	53	50	100	Crocin	sMet	Cholesterol, TG, LDL, HDL
11	Javandoost	Iran	2017	8	22	22	38	40	30	Crocin	sMet	Cholesterol, TG, LDL, HDL
12	Jafarnia	Iran	2017	6	20	20	29	32	450	Saffron	CAD	Weight
13	Gout	France	2010	8	30	29	36	36	176.5	Satiereal	healthy	Weight
14	Fadai	Iran	2014	12	20	21	49	48	30	Saffron	Schizophrenia	Cholesterol, TG, LDL, HDL
15	Fadai	Iran	2014	12	20	21	48	48	30	Crocin	Schizophrenia	Cholesterol, TG, LDL, HDL
16	Azimi	Iran	2014	8	42	39	57	55	1000	Saffron	DM	Weight, Cholesterol, TG, LDL, HDL
17	Abedimanesh, N.	Iran	2017	8	25	25	56	56	30	Saffron	CAD	Weight, Cholesterol, TG, LDL, HDL
18	Abedimanesh, N.	Iran	2017	8	25	25	53	56	30	Crocin	CAD	Weight, Cholesterol, TG, LDL, HDL

TG = Triacylglycerol; LDL = Low density lipoprotein; HDL = High-density lipoprotein; METs = Metabolic equivalents; DM= Diabetes; CAD= Cardiovascular disease; Int= intervention; Plc= placebo; sMet=Syndrome Metabolic.

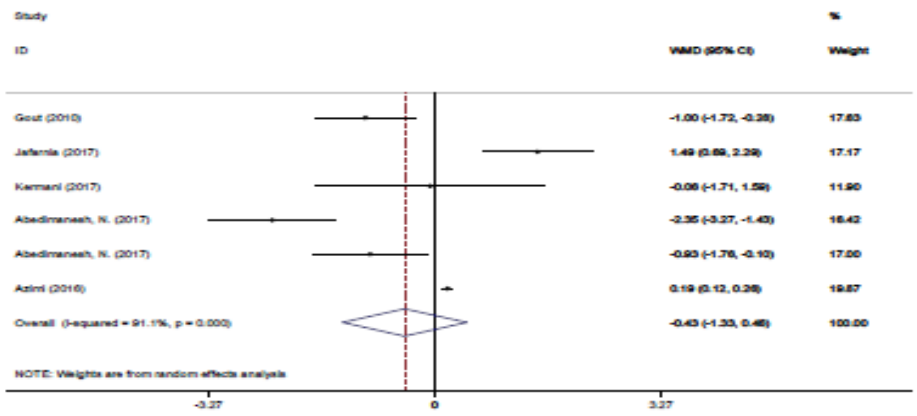
Table 2. Quality of included studies

Study	Random sequence generation selection bias	Allocation concealment selection bias	Selective reporting	Other bias	Blinding performance bias	Blinding outcome detection bias	Incomplete outcome data	Ahrq standards
Sepahi, 2018	Low	Low	Low	Low	Low	Low	Low	GOOD
Sepahi, 2018	Low	Low	Low	Low	Low	Low	Low	GOOD
Nikbakht-Jam, 2016	Unclear	Unclear	Low	Low	Low	Low	Low	FAIR
Mohamadpour, 2013	Unclear	Unclear	Low	Low	Low	Low	Low	FAIR
Modaghegh, 2008	Unclear	Unclear	Low	Low	Low	Low	Low	FAIR
Modaghegh, 2008	Unclear	Unclear	Low	Low	Low	Low	Low	FAIR
Milajerdi, 2018	Low	Low	Low	Low	Low	Low	Low	GOOD
Mansoori, 2011	Low	Low	Low	Low	Low	Low	Low	GOOD
Kermani, 2017	Low	Low	Low	Low	Low	Low	Low	GOOD
Kermani, 2017	Low	Low	Low	Low	Low	Low	Low	GOOD
Javandoost, 2017	Low	Low	Low	Low	Low	Low	Low	GOOD
Jafarnia, 2017	Low	Low	Low	Low	Low	Low	Low	GOOD
Gout, 2010	Low	Low	Low	Low	Low	Low	Low	GOOD
Fadai, 2014	Low	Low	Low	Low	Low	Low	Low	GOOD
Fadai, 2014	Low	Low	Low	Low	Low	Low	Low	GOOD
Azimi, 2014	Low	Low	Low	Low	High	High	Low	POOR
Abedimanesh, 2017	Low	Low	Low	Low	Low	Low	Low	GOOD
Abedimanesh, 2017	Low	Low	Low	Low	Low	Low	Low	GOOD

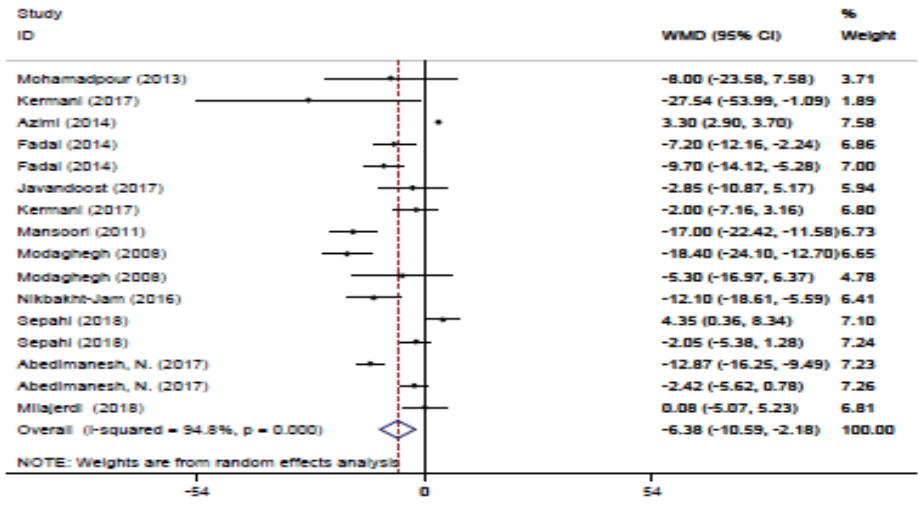
Table 3. Results of subgroup analysis of included randomized controlled trials in meta-analysis

Variables	Type		All
	Saffron	Crocin	-
Weight			
Number of studies	4	1	6
weighted mean difference (WMD)	-0.16	-0.93	-0.43
95% CI	-1.46, 1.14	-1.75, -0.10	-1.33, 0.46
p-heterogeneity, I2%	0.001, 92.4	-	0.001, 91.1
Cholesterol			
Number of studies	8	8	16
weighted mean difference (WMD)	-9.27	-3.73	-6.38
95% CI	-17.32, -1.21	-7.41, -0.06	-10.58, -2.18
p-heterogeneity	0.001, 96.8	0.001, 76.9	0.001, 94.8
TG			
Number of studies	8	8	16
weighted mean difference (WMD)	-11.36	-0.42	-5.37
95% CI	-19.64, -3.07	-6.07, 5.21	-10.25, -0.48
p-heterogeneity	0.001, 93.5	0.004, 66.6	0.001, 88.8
LDL			
Number of studies	7	8	15
weighted mean difference (WMD)	-1.83	-4.56	-3.03
95% CI	-8.07, 4.41	-9.91, 0.77	-6.53, 0.47
p-heterogeneity	0.001, 91.9	0.001, 90.1	0.001, 91.6
HDL			
Number of studies	7	8	15
weighted mean difference (WMD)	0.87	0.49	0.91
95% CI	-1.81, 3.57	-0.95, 1.94	-0.13, 1.96
p-heterogeneity	0.001, 96.7	0.001, 94.4	0.01, 95.4

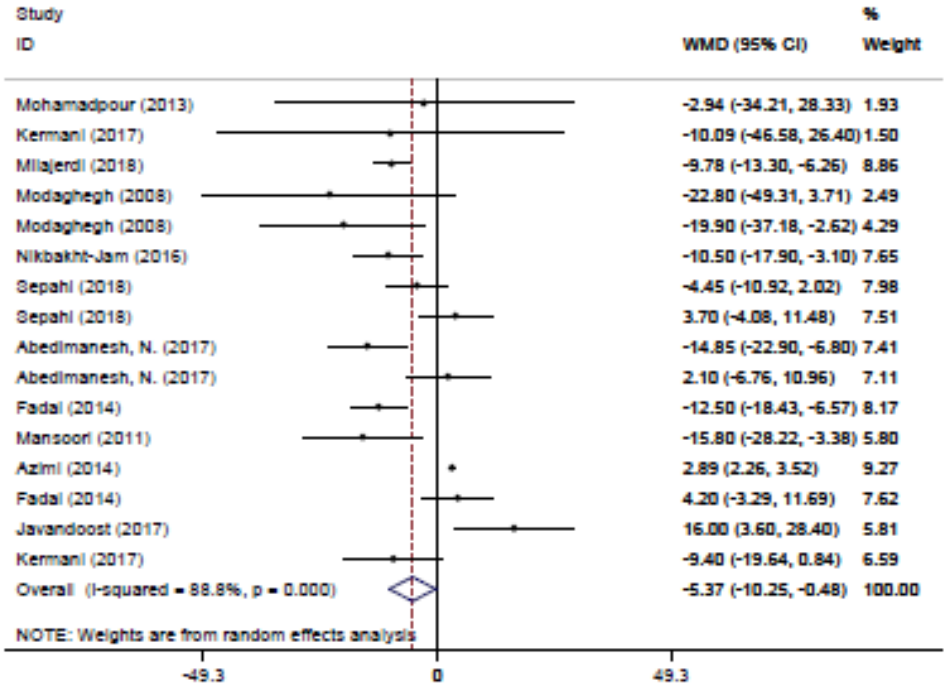
A) Weight



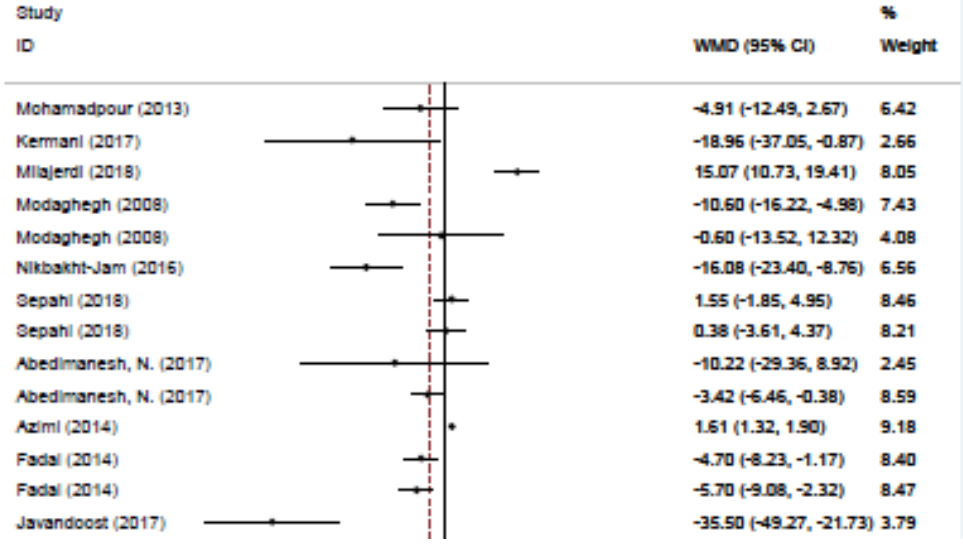
B) Cholesterol



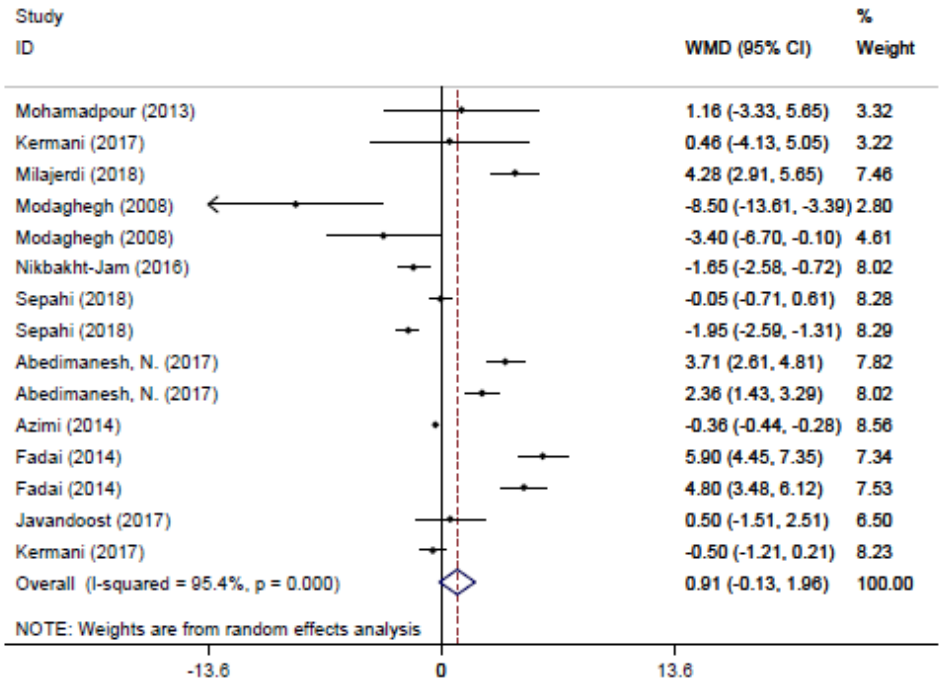
C) TG


Study
ID
WMD (95% CI)
%
Weight
Mohamadpour (2013) -2.94 (-34.21, 28.33) 1.93
Kermani (2017) -10.09 (-46.58, 26.40) 1.50
Milajerdi (2018) -9.78 (-13.30, -6.26) 8.86
Modaghegh (2008) -22.80 (-49.31, 3.71) 2.49
Modaghegh (2008) -19.90 (-37.18, -2.62) 4.29
Nikbakht-Jam (2016) -10.50 (-17.90, -3.10) 7.65
Sepahi (2018) -4.45 (-10.92, 2.02) 7.98
Sepahi (2018) 3.70 (-4.08, 11.48) 7.51
Abedimanesh, N. (2017) -14.85 (-22.90, -6.80) 7.41
Abedimanesh, N. (2017) 2.10 (-6.76, 10.96) 7.11
Fadal (2014) -12.50 (-18.43, -6.57) 8.17
Mansoori (2011) -15.80 (-28.22, -3.38) 5.80
Azimi (2014) 2.89 (2.26, 3.52) 9.27
Fadal (2014) 4.20 (-3.29, 11.69) 7.62
Javandoost (2017) 16.00 (3.60, 28.40) 5.81
Kermani (2017) -9.40 (-19.64, 0.84) 6.59
Overall (I-squared = 88.8%, p = 0.000) -5.37 (-10.25, -0.48) 100.00
NOTE: Weights are from random effects analysis
-49.3
0
49.3

D) LDL


Study
ID
WMD (95% CI)
%
Weight
Mohamadpour (2013) -4.91 (-12.49, 2.67) 6.42
Kermani (2017) -18.96 (-37.05, -0.87) 2.66
Milajerdi (2018) 15.07 (10.73, 19.41) 8.05
Modaghegh (2008) -10.60 (-16.22, -4.98) 7.43
Modaghegh (2008) -0.60 (-13.52, 12.32) 4.08
Nikbakht-Jam (2016) -16.08 (-23.40, -8.76) 6.56
Sepahi (2018) 1.55 (-1.85, 4.95) 8.46
Sepahi (2018) 0.38 (-3.61, 4.37) 8.21
Abedimanesh, N. (2017) -10.22 (-29.36, 8.92) 2.45
Abedimanesh, N. (2017) -3.42 (-6.46, -0.38) 8.59
Azimi (2014) 1.61 (1.32, 1.90) 9.18
Fadal (2014) -4.70 (-8.23, -1.17) 8.40
Fadal (2014) -5.70 (-9.08, -2.32) 8.47
Javandoost (2017) -35.50 (-49.27, -21.73) 3.79

E) HDL


Study
ID
WMD (95% CI)
%
Weight
Mohamadpour (2013) 1.16 (-3.33, 5.65) 3.32
Kermani (2017) 0.46 (-4.13, 5.05) 3.22
Milajerdi (2018) 4.28 (2.91, 5.65) 7.46
Modaghegh (2008) -8.50 (-13.61, -3.39) 2.80
Modaghegh (2008) -3.40 (-6.70, -0.10) 4.61
Nikbakht-Jam (2016) -1.65 (-2.58, -0.72) 8.02
Sepahi (2018) -0.05 (-0.71, 0.61) 8.28
Sepahi (2018) -1.95 (-2.59, -1.31) 8.29
Abedimanesh, N. (2017) 3.71 (2.61, 4.81) 7.82
Abedimanesh, N. (2017) 2.36 (1.43, 3.29) 8.02
Azimi (2014) -0.36 (-0.44, -0.28) 8.56
Fadai (2014) 5.90 (4.45, 7.35) 7.34
Fadai (2014) 4.80 (3.48, 6.12) 7.53
Javandoost (2017) 0.50 (-1.51, 2.51) 6.50
Kermani (2017) -0.50 (-1.21, 0.21) 8.23
Overall (I-squared = 95.4%, p = 0.000) 0.91 (-0.13, 1.96) 100.00
NOTE: Weights are from random effects analysis
-13.6
0
13.6